

# New Insights on Age-Related Hearing Loss

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Currently, more than 37 million Americans have impaired hearing and approximately 75% of these persons are over the age of 55. More than 30 years ago, a multidisciplinary team of researchers including audiologists, histopathologists, biochemists, and electrophysiologists was brought together to study the causes of age-related hearing loss. Since its inception, this National Institutes of Health funded Clinical Research Center has included research projects headed by investigators from the Department of Otolaryngology-Head and Neck Surgery and the Department of Pathology and Laboratory Medicine at the Medical University of South Carolina (MUSC).

Age-related hearing loss is a difficult problem to study because many factors can result in hearing loss in older persons, such as the accumulated effects of exposure to noise, ototoxic drugs, or certain diseases, making it difficult to distinguish these factors from the effects of age. Early studies with animal models of age-related hearing loss conducted in our Center were designed to control the most pertinent variables for systematic studies of pathology, physiology, and chemistry at the cellular and molecular levels. One goal of our research has been use this information to understand potential mechanisms of hearing loss in older humans, where confounding environmental effects cannot be controlled. In past studies, gerbils were raised throughout their lifespan (3+ years) under experimental conditions wherein environmental variables (temperature, humidity, air quality, noise), diet, and drugs are strictly controlled. Thus, pathological changes and hearing loss in these "quiet-aged" gerbils relate only to the aging process.

Gerbils raised under these conditions show very specific changes with age, including a metabolic component to age-related hearing loss, or presbycusis. Metabolic presbycusis is associated with a decline in the endocochlear potential (EP), an electrical potential of 80-100 mV in the cochlea, which acts like a battery to drive auditory transduction. In addition, age-related declines were observed in auditory function, including a flat 10-40 dB hearing loss in the lower frequencies with hearing loss at higher frequencies gradually increasing to ~60 dB, preservation of (but reduced) cochlear nonlinearities such as otoacoustic emissions (OAEs), and primary degeneration of spiral ganglion neurons. Absent are age-related losses of outer and inner hair cells, except scattered losses in the most apical and basal regions of the cochlea. Thus, gerbils raised in quiet exhibit all the characteristics of *metabolic presbycusis*.

A second source of pathology seen in quiet-aged gerbils is primary degeneration of about 10-15% of the spiral ganglion neurons across the entire cochlear duct, which occurs in the presence of an intact population of inner hair cells (Mills et al., 2006). Age-related neural degeneration is correlated with strial degeneration and the resulting loss of the endocochlear potential or EP (Lang et al., 2010), suggesting a role for the EP in maintaining synchronized neural firing and viability. Among the most prominent changes in the physiological properties of quiet-aged gerbils are decreases in the slope of the input-output function of the compound action potential (CAP). With little change in neural thresholds (e.g., amplitude of responses to lower level signals), a reduction in CAP amplitudes with higher level signals may relate to poorly synchronized activity of individual nerve fibers. In quiet-aged gerbils, these are characteristics of *neural presbycusis*.

Neural presbycusis is the least understood of the subcategories of age-related hearing loss, because the mechanisms underlying neural loss and shrinkage with age have not been determined. Findings from quiet-aged gerbils would predict age-related reductions in auditory functions that are dependent on synchronous neural responses, such as temporal information coded by neural phase locking. However, the predicted effects of neural presbycusis have not been confirmed in aging human subjects, specifically those with near-normal auditory detection

thresholds. Without knowledge of its functional effects in older humans, the clinical significance of neural presbycusis remains largely unknown.

In contrast to changes in the inner ear due to pure aging, hearing loss resulting from sensory cell loss is associated with a steeply sloping high-frequency hearing loss, loss of cochlear nonlinearities (OAEs), broadened tuning, and secondary neural degeneration associated with injury to inner hair cells (*sensory presbycusis*). These changes are most often seen following exposure to excessive noise or ototoxic drugs, rather than as a result of aging.

What is the evidence that metabolic presbycusis underlies the characteristic gradually sloping audiogram of aging gerbils (and humans)? In **Figure 1**, threshold shifts in the CAP of the auditory nerve are shown (solid lines) for younger gerbils whose EP was reduced by the application of furosemide (Schmiedt et al., 2002; Schmiedt, 2010). These changes in CAP are compared to pure-tone thresholds (symbols and lines) in non-noise exposed older adults from a sample reported by Jerger et al. (1993), and from the large database of MUSC's 30-year longitudinal study of age-related hearing loss. In parallel studies to studies with animal models, over the past 30 years investigators in the Clinical Research Center have collected audiometric, cognitive, and medical/biological data from more than 1,600 adults of all ages. The correspondence between threshold shifts produced in gerbil and hearing loss of aging humans suggests a common mechanism, namely a reduction in the EP that effectively reduces the voltage available to the cochlear amplifier (Schmiedt et al., 2002). Thus, our hypothesis is that age-related hearing loss as shown by the audiogram can be best explained by age-related pathology of the cochlear lateral wall with attendant changes in potassium recycling mechanisms and reductions in the EP, which deprive the cochlear amplifier of its essential power supply. This hypothesis predicts that age-related declines in hearing as indicated by the audiogram are largely explained by pathology of the auditory periphery.

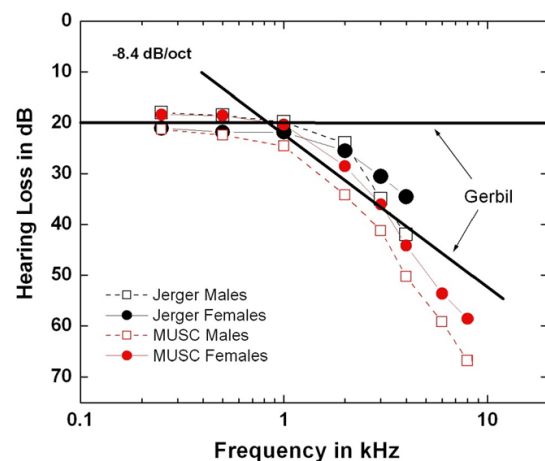


Figure 1. Age-related hearing loss in two groups of older human subjects with no history of noise exposure are compared to threshold shifts of the compound action potential in laboratory animals where the endocochlear potential (EP) has been reduced by the application of furosemide (Schmiedt et al., 2002; Schmiedt, 2010).

As a further test of this hypothesis, we examined the extent to which unique and consistent patterns of “audiometric phenotypes” can be identified from pure-tone audiograms in a large sample of older adults (Dubno et al., 2013). Schematic boundaries of audiograms were defined based on four hypothesized conditions of cochlear pathology obtained from results from animal models. As shown in **Figure 2**, the four audiometric phenotypes are: (1) older normal; (2) metabolic presbycusis; (3) sensory presbycusis; and (4) a mixed phenotype of metabolic + sensory presbycusis.

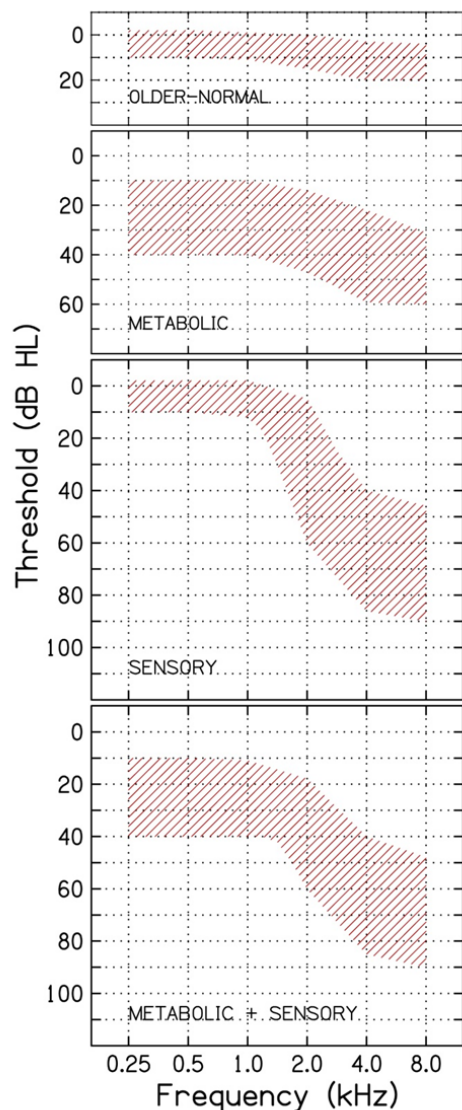


Figure 2. Shaded regions representing ranges of audiograms corresponding to four phenotypes of age-related hearing loss (Dubno et al., 2013; Schmiedt, 2010).

Next, audiograms of research participants (age >50) stored in the MUSC database were searched for “exemplars” (best examples) of these phenotypes, without knowledge of demographic information (N=1,728). Audiograms from 374 ears were identified as exemplars of one of the four phenotypes; the mean audiogram for each phenotype is shown in **Figure 3**. Audiograms of the older-normal phenotype (gray) show generally normal hearing, with a “pre-metabolic” characteristic in the higher frequencies. Similar to Figure 1, audiograms of the metabolic phenotype (green) have a flat loss of ~20 dB in the lower frequencies and a gradually sloping loss in the higher frequencies. Audiograms of the sensory phenotype (red) have generally normal hearing in the lower

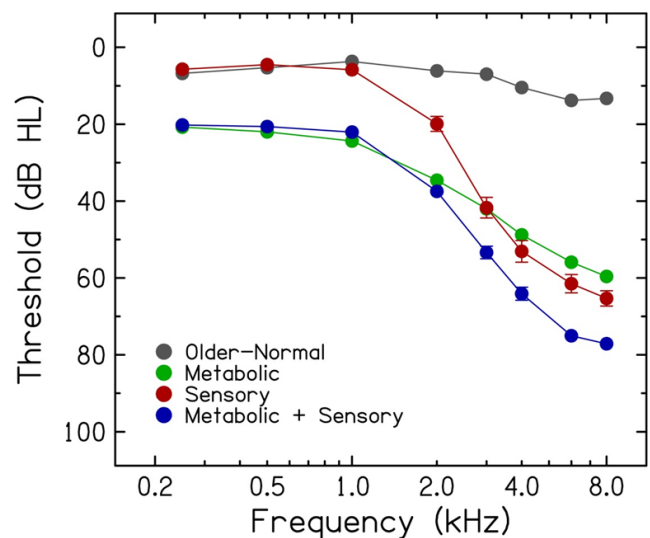


Figure 3. Mean audiograms from 374 ears from the MUSC database identified as exemplars (best examples) of one of four audiometric phenotypes (Dubno et al., 2013).

frequencies and a steeply sloping loss in the higher frequencies. Audiograms with the mixed phenotype of metabolic+sensory (blue) have characteristics of metabolic presbycusis in the lower frequencies and sensory presbycusis in the higher frequencies.

To provide external validity of the four phenotypes, distributions of age, sex, and noise exposure history were determined. As predicted, subjects whose audiograms were exemplars of the older normal phenotype tended to be younger (among older adults), mostly female, with negative noise histories. Subjects in the metabolic phenotype were generally older, predominantly female, with negative noise histories. Subjects in the sensory phenotype were younger, mostly male, with positive noise histories. Subjects in the mixed phenotype were older, predominantly male, with positive noise histories.

As an additional test of validity and reliability, phenotypes of the exemplar audiograms were predicted using statistical methods (e.g., machine learning, quadratic discriminant analysis). These tools were used to develop classifiers, which estimate the probability that newly obtained audiograms exhibit one of the four phenotypes. The automated procedures classified the exemplars with 88-91% accuracy, with a majority of the misclassifications occurring between the metabolic and mixed phenotypes. Finally, phenotypes of non-exemplar audiograms (N=1,354) were predicted using the same automated methods; classification was determined by the highest probability estimate. Within each phenotype, audiogram shapes of exemplar and non-exemplar cases were generally similar across frequency. Non-exemplar cases were consistent with exemplar cases with respect to their distributions of ages, genders, and noise histories.

Subsequently, information from the MUSC database have further defined the phenotypes by identifying characteristics beyond the audiogram that differentiate subjects, including longitudinal changes in hearing (Vaden et al., 2017) and transient-evoked otoacoustic emissions, which is a measure of the health of the outer hair cells (Vaden et al., 2018).

In summary, results to date suggest that animal models can be used to predict human cochlear pathology using audiograms and more advanced measures of auditory function. Human audiometric phenotypes appear consistent with predictions from animal findings associated with sensory and strial pathology. Future studies will explore if this approach may be applied to understanding neural presbycusis. Finally, in the absence of confounding factors such as noise and drug exposures, audiometric phenotypes are consistent with the view of age-related hearing loss as a metabolic, vascular, neural disorder rather than a sensory disorder.

## Acknowledgements

This work was supported (in part) by research grant P50 DC000422 from NIH/NIDCD and by the South Carolina Clinical and Translational Research (SCTR) Institute, with an academic home at the Medical University of South Carolina, NIH/NCRR Grant number UL1 RR029882. This work was conducted in a facility constructed with support from Research Facilities Improvement Program Grant Number C06 RR14516 from the National Center for Research Resources, National Institutes of Health. The significant contributions of principal investigators Mark A. Eckert, Hainan Lang, John H. Mills, Richard A. Schmiedt, and Bradley A. Schulte are gratefully acknowledged.

## Notes and References

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